IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Our Ref: 1038-384 MIS:jb

In re patent application

No.:	08/286,189
Applicant:	Sonia E. Sanhueza, et al.
Title:	INACTIVATED RESPIRATORY SYNCYTIAL VIRAL VACCINES
Filed:	August 5, 1994
Group No.:	1641
Examiner:	J. Parkin

DECLARATION UNDER 37 C.F.R. 1.136(b)

I, Professor Gregory A. Prince of 14800 Pettit Way, Potomac, Maryland 20854, USA, hereby declare as follows:

1. I am currently President and CEO of Virion Systems Inc. and Clinical Assistant Professor of Pathology at the University of California, as well as Research Professor of Paediatrics at the Uniformed Services University of the Health Sciences, Baltimore. I have been actively involved in research in the field of animal models for RSV infection in humans and in particular the cotton rat model since 1973. I have published approximately 61 papers in total on RSV, 58 of which deal with RSV in the cotton rat. A copy of my CV is attached as Exhibit I.

2. I have been asked to describe the attitude of the scientific community to the cotton rat model of RSV infection in man before the effective filing date of this patent application. To provide such description, I would like to the following matters: (1) the biomedical uses of the cotton rat model of human diseases in general; (2) the predictive value of the cotton rat models of infectious disease; and (3) the comparison of the cotton rat model with other models of RSV infection.

3. Biomedical uses of the cotton rat as a relevant model of many human diseases

3.1 The cotton rat (*Sigmodon* species) is a relevant animal model of many human infectious diseases. Most recently it was directly responsible for the development of two immunoglobulin products for the prevention of respiratory syncytial virus (RSV) disease. These products are currently being administered to over 100,000 high-risk infants annually.

3.2 The first biomedical use of cotton rats occurred in the late 1930s, when Charles Armstrong of the National Institute of Health (USA) observed paralytic disease in a cotton rat following injection of a spiral cord homogenate from a boy who died form poliomyatitis. For over a decade the cotton rat was the principal animal model of polio. Since 1938, to my personal knowledge, it has been shown to be susceptible to a remarkably broad spectrum of pathogens affecting humans, including tuberculesis, *Mycoplasma pneumoniae*, epiderric typhus, endemie typhus. Venezuelan equine encephalitis. Rocky mountain spotted fever, respiratory syncytial virus, Rift Valley fever virus, human parainfluenza viruses types 1, 2 and 3, human adenoviruses types 2, 5, 7 and 8, herpes simplex virus type 1, *Borrelia burgdorferi* (Lyme disease), human influenza viruses types A and B, measles virus, Guanarito virus (Venezauelan hemorrhagic fever). Black Creek Canal virus (hantavirus) and human immunodeficiency virus type 1. This is in marked contrast to other animals such as laboratory rats, which can often not be infected by human pathogens. I have not discussed the relevant references that support my statements above, but stand prepared to do so if requested.

4. <u>Prediction value of the cotton rat models of infectious diseases</u>

4.1 The utility of the cotton rat in predicting results of human studies is most notable concerning the ability of anti-RSV immunoglobulin to protect against RSV disease. This observation, first made in cotton rats (Prince et al., 1983, Exhibit II) was the foundation that led to the development of two licensed RSV prophylaxis drugs, RespiGam® and Synagis® (Medimmune, Inc., Gaithersburg, Maryland). In order to appreciate the value of the cotton rat in the development of these two drugs. It s essential to understand that conventional wisdom at that time taught that RSV antibody was harmful, an assertion first published in 1970 (Chanock et al., 1970 (Exhibit III). Quantitative studies in our laboratory showed that cotton rats could be protected from pulmonary infection if plasma RSV neutralizing antibody titers of 1:350 or greater were

achieved (Prince et al., 1985, Exhibit IV), and that there was no evidence of disease exacerbation, an important finding given the conventional wisdom of the time.

4.2 On the strength of the cotton rat data, Dr. Carole Heilman of the National Institutes of Health (USA) proposed NIH funding of a clinical trial of RSV prophylaxis in high risk infants using immunoglobulin. In March 1988, NIH issued a Request for Proposal, and later that year a team led by Dr. Val Hemming was awarded a contract to conduct clinical trials. Using as a target the very titer of anti-RSV antibody shown to be protective in cotton rats, this group carried out successful clinical trials of passive IgG prophylaxis of RSV disease in high-risk infants, which led to the licensure of the first RSV prophylaxis drug, RespiGam® (Groothuis et al., 1993, Exhibit V). In this and subsequent immunoglobulin studies, it is important to note that the United States Food and Drug Administration was sufficiently confident of the results of cotton rat experiments that they allowed progression to human clinical trials without requiring testing in a non-human primate.

4.3 A further example comes from our study reporting a prophylactic effect of immunoglobulin which also showed that immunoglobulin given to animals previously infected with RSV dramatically reduced viral titers within hours (Prince et al., 1983, Exhibit II referred to above). On the strength of this observation, we conducted therapeutic trials (Hemming et al., 1987, Exhibit VI). The therapeutic trials confirmed what the cotton rat had shown that immunoglobulin reduced viral titers. [These trials differed from the subsequent trials that led to RespiGam® and Synagis® in that infants were treated with immunoglobulin after being admitted to the hospital with confirmed RSV disease, whereas the later studies involved administration of immunoglobulin as a preventive. The therapeutic trial confirmed that the cotton rat had shown that immunoglobulin reduced viral titers. However, there was no significant improvement in the clinical status of the patients. Subsequent clinical

trials of therapeutic anti-RSV immunoglobulins, both polyclonal and monoclonal, have confirmed that this approach is safe and reduces viral titers, but is ineffective in improving the clinical status of the patients. Studies in cotton rats provided an explanation for these results, indicating that reversal of pulmonary disease requires an antiviral agent (such as immunoglobulin) to eliminate virus *plus* an anti-inflammatory agent to reverse pulmonary inflammation. Again the experience in cotton rats mirrored the outcome in humans]

4.4 The Cotton Rat Model was also a successful model in predicting the efficacy of an antiviral compound, Ribavirin, against RSV infection. The effect of Ribavirin on RSV infection was shown in a 1982 Hruska paper (Exhibit VII) describing parenteral and aerosol treatment of RSV-infected cotton rats. Shortly thereafter, with no testing in primates, ribavirin was taken into clinical trials as described in Hall, 1983 (Exhibit VIII). Thus, again the cotton rat model provided an accurate prediction of human RSV disease.

5. Comparison of the cotton rat with other models of RSV

5.1 It is worth noting that no RSV clinical trial, and significantly, neither of the currently licensed RSV immunoglobulin products, relied at all on a primate model. Indeed even chimpanzees, the closest relative of humans, have not correctly predicted the outcome of clinical trials of a candidate RSV vaccine. There are no publications in peer-reviewed scientific journals concerning RSV vaccines in baboons whereas over 100 published papers have supported use of the cotton rat in terms of sheer numbers. Virion Systems, Inc. has used about 40,000 cotton rats over the past decade and over the same time period over 150,000 infants have received the drugs developed by the use of the cotton rats predictive model.

6. Having regard to the above and the information presented in the attached Exhibits, it is my opinion that the cotton rat model was seen by the scientific

community in 1987 as a useful and predictive model of RSV infection in man. Published reports had demonstrated a very close correlation between results obtained in cotton rats and in human clinical trials. As noted earlier, the NIH were prepared to fund human clinical trials based on cotton rats.

7. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Declared at

On day of , 2002.

_____

Gregory A. Prince (Professor)